

Early Diagnostic and Prognostic Value of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Critically Ill Children With Septic Acute Kidney Injury

Mohamed A El-Gamasy¹, Samir M Hasan² Wageih S El-Naghy³

¹MD Pediatrics, Assistant Professor of Pediatrics, Faculty of Medicine, Tanta University, Egypt.

²Lecturer of Pediatrics, Faculty of Medicine, Tanta University, Egypt

³MD Medical Microbiology and Immunology, Assistant Professor of Medical Microbiology and Immunology, Faculty of Medicine, Tanta University, Egypt.

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*Corresponding author: Mohamed A. El-Gamasy, MD Pediatrics, Assistant Professor of Pediatrics, Faculty of Medicine, Tanta University, Egypt, Tel: +2 01208136076; E-mail: mgamsy@gmail.com

Abstract

Background: Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a biomarker of acute kidney injury (AKI) even on top of chronic kidney disease.

Objectives: was to determine NGAL levels in children as early diagnostic and prognostic factor for AKI in critically ill children with sepsis.

Subjects and Methods: The present study was carried out on 120 children with sepsis admitted in Pediatric Intensive care Unit of Tanta University Hospital. They were subdividing into 3 groups, Group (1): 45 sepsis–non-AKI, Group (2): 45 sepsis with AKI. Group (3) 30 non sepsis–non-AKI as controls. Urine samples were collected daily for 5 days from the sepsis patients and urinary NGAL levels were measured by ELISA test for group 1 on the admission day and on day 5 after admission while in group 2 on the admission day 24 h before the onset of AKI, and on the day of AKI onset while in group 3, on the admission day.

Results: There was a significant increase in urinary NGAL levels in sepsis patients (groups 1 & 2) when compared with non sepsis patients (14.8 ± 4.2 and 5.5 ± 2.6 ng/ml, respectively; $P < 0.001$). ROC curve of NGAL reported that in sepsis patients who developed AKI (group 2), urinary NGAL preceded the rise in serum creatinine, and at its cutoff level of 33.1 ng/ml it predicted AKI with an area AUC of 0.96, sensitivity of 99%, and specificity of 85%; at its cutoff level of 48.7 ng/ml, it predicted the need for dialysis with AUC of 0.81, sensitivity of 84%, and specificity of 73%. Urine NGAL could not predict mortality among sepsis patients.

Conclusion: Urinary NGAL can predict AKI well in critically ill septic pediatric patients and can predict their indication for dialysis.

Keywords: Acute Kidney Injury Prediction; Neutrophil Gelatinase-Associated Lipocalin; Sepsis;

Introduction

Sepsis is considered a primary cause of morbidity and mortality in patients admitted to ICUs [1,2,3]. The urine has yielded promising markers for the early detection of AKI even on top of chronic kidney disease [4]. They include, Cystatin C, Microalbuminuria, N-acetyl- β -glucosaminidase (NAG), Interleukin-18, Fetuin, Retinol Binding Protein (RBP), clusterin, Cysteine Rich Protein and Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) [5,6,7,8,9,10,11]. Neutrophil Gelatinase-Associated Lipocalin (NGAL) which is a member of the lipocalin superfamily expressed by neutrophils and various epithelial cells, is one of the most frequently investigated for early diagnosis of AKI [12,13]. NGAL is also a marker for prognosis of AKI, where uNGAL correlates with the degree of AKI and significantly increases in patients with progressive but not stable kidney failure [14,15]. Also, uNGAL as a predictive biomarker of nephrotoxicity was confirmed in patients with contrast induced nephrotoxicity and cisplatin nephropathy [15,16]. uNGAL levels were significantly elevated in children with decreased glomerular filtration rate (GFR) [17].

The aim of the present work

was to validate the use of urinary NGAL as a prognostic factor for the early prediction of AKI development, dialysis need, and mortality in a cohort study of children with sepsis

Materials and Methods

Design of the study and Setting

The present prospective cohort study was carried out after approval from research ethical committee centers of Tanta University Hospital and obtaining an informed oral or written consents from parents of included children.

Inclusion criteria

90 patients with sepsis admitted in Pediatric Intensive care

unit (NICU) and Pediatric Nephrology unit of Tanta University Hospital and 30 children of the same age and sex without sepsis or AKI served as control group.

The subjects were subdivided into 3 groups

Group (1): 45 patients with sepsis with no AKI. *Group (2):* included 45 patients with sepsis and AKI. *Group (3):* 30 non-sepsis, non-AKI patients as the control group).

All children admitted in PICU of Tanta university hospitals from November 2016 to November 2017 were included.

Exclusion criteria

Pediatric patients who were known to have chronic kidney disease, patients with AKI on admission, patients with prerenal and postrenal causes of AKI, patients with nonseptic AKI, and patients exposed to radiocontrast dye or nephrotoxic drugs (aminoglycoside, colistin, or amphotericin) within at least 1 week before admission.

Chronic kidney disease was defined on the basis of the definition of National Kidney Foundation as kidney damage or glomerular filtration rate less than 60ml/min/1.73m² for 3 or more months, irrespective of the cause [18].

Sepsis and septic shock were diagnosed according to the guidelines of the International Sepsis Definitions Conference [19]. AKI was diagnosed according to Risk, Injury, Failure, Loss, and end stage renal disease (ESRD) (RIFLE) criteria. Urine output was closely monitored every hour, and daily assessment of serum creatinine and its change in relation to its baseline levels on admission (if normal) was carried out [20].

All patients and controls were subjected to the following:

- **History Taking:** about age, sex and admission diagnosis, duration of hospital stay and drugs.
- **Clinical Examination:** included body weight, oedema and vital signs (heart rate, temperature, mean arterial blood pressure) which were assessed for the evaluation of sepsis .
- **Laboratory Investigations:** which included on admission, baseline serum creatinine and blood urea Nitrogen(BUN) levels, Complete blood counting (CBC), C-reactive protein, 24 hour urinary collection for volume and protein estimation.
- Serum creatinine was assessed in spot blood samples obtained on admission and then reassessed daily at constant intervals (every 24 h) for 5 days in sepsis patients (groups 1 and 2). Simultaneously, urine samples were collected on the day of admission from all involved patients by clean catch mid stream voids or from inserted indwelling Foley catheters. Urine samples were collected daily for 5 days from sepsis patients (groups 1 and 2). In sepsis-AKI patients (group 2) sample collection was stopped at the onset of AKI.
- Urinary NGAL level was assessed by ELISA kit only in selected samples .It was measured in group 1 from samples taken on admission day and on day 5. In group 2, it was measured from

samples taken on admission day, from samples collected 24 h before the onset of AKI (1 day before AKI), and from samples taken on the day of AKI onset. In group 3, it was measured from samples taken on the admission day only. [21]

Sampling for laboratory investigations:

About 6 ml venous blood sample was withdrawn from patients and controls, 2 ml blood sample was used for CBC estimation through using EDTA vacutainer tubes and the remainder of blood were put into plain tubes for centrifugation and separation of serum which used for estimation of urea, and creatinine levels. Morning urine sample from patients were collected by one of two techniques, either clean catch mid stream method or urinary Catheterization method using 8 French polyethylene feeding tube to collected into sterile container and centrifuged for about 20 minutes. After being centrifuged at 5000b p m for 15min, the urine and blood supernatant samples were frozen within 2 h of collection at -80°C till the time of NGAL assay. Another 24-hour urine collection was used for estimation of urine protein /24 hr collection. Samples were thawed and mixed thoroughly just before the assay to avoid erroneous results of repeated freeze/thaw cycles [21]. Other 24-hour urine collection samples were kept into sterile containers at refrigerator at degree from 2 to 8 degrees Celsius and then the samples were re-warmed to room temperature just before urinary assessment and urine protein /24 hr collection.

Severity of illness in the first 24 hours of admission was assessed by Pediatric Risk of Mortality score (PRISM III), length of hospital stay was recorded and the follow up was with the Sequential Organ Failure Assessment (SOFA) score for outcome [22,23]

Statistical Analysis:

Data were statistically described in terms of mean \pm SD, frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between the study groups was done using the Student t-test for independent samples. For comparing categorical data, the X²-test was performed. The exact test was used instead when the expected frequency was less than 5. Correlation between variables was determined using Pearson's moment correlation equation for linear relation. Accuracy was represented using the terms sensitivity and specificity. A P value less than 0.05 was considered statistically significant. All statistical calculations were performed using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, New York, USA) and statistical package for the social science (SPSS, version 15 for Microsoft Windows; SPSS Inc., Chicago, Illinois, USA). Receiver operator characteristic (ROC) analysis was used to determine the optimum cutoff value for the studied diagnostic markers as follows: the best possible biomarker of a disease process would plot a point in the upper left corner of the ROC space, which would represent 100% sensitivity (all true positives detected) and 100% specificity (no false positives found). An area under the curve (AUC) of 1.0 represents a perfect biomarker, whereas an AUC of 0.5 (as would be derived from the line of no discrimination) indicates a result that is no better than

expected by random chance. An AUC of 0.75 or above is generally considered a good biomarker, and an AUC of 0.9 or above would represent an excellent biomarker.

Results

The demographic, clinical and laboratory data of the involved patients were summarized in (Table 1). Out of the 120 patients with sepsis, pneumonia was the main source of sepsis (41 patients, 45.5 %)[24]. During their PICU course, 40 (44.4 %) patients developed septic shock, 45 (50%) patients developed AKI within their first 5 days of PICU stay, and 37 (41.1%) of the last group required dialysis. Patients with sepsis and AKI had higher mean value of PRISM score but without statistical significance, Group 2 has also statistically significant longer PICU stay and higher mortality rate than group 1 (Table 1). Initial

uNGAL values In collected on the day of admission, urine NGAL was significantly higher in sepsis patients (groups 1 and 2) than in non sepsis patients (group 3) (14.8 ± 4.2 and 5.5 ± 2.6 ng/ml, respectively; $P < 0.001$) (Table 2). However, within these sepsis patients, urine NGAL on admission was not significantly different between patients who developed AKI in their first 5 days of ICU stay (group 2) and others who did not develop AKI (group 1) (16.8 ± 4.3 and 13.5 ± 4.6 ng/ml, respectively; $P = 0.32$) (Table 2). As regard Ungal in group 1 on admission day and At 5 days after admission, urinary NGAL did not change significantly (13.5 ± 4.6 and 15.3 ± 3.3 ng/ml, respectively; $P = 0.08$) (Table 2). However, regarding follow up of uNGAL in group 2 within 5 days of admission, there was a significant progressive rise in urine NGAL values in samples collected 1 day before onset of AKI and on the day of onset of AKI than on admission (16.8 ± 4.3 , 40.1 ± 11.7 ,

Table 1: Demographic, clinical and laboratory data in studied subjects.

	Group 1 Sepsis (No = 45)	Group 2 Septic AKI (No = 45)	Control (No=30)	Statistical test	P value
Age distribution at time of study (years)					
range	1.5-9 years	2 -10 years	1.5 -10 years	ANOVA(F)	0.05
Mean \pm SD	4.47 \pm 2.16	6.63 \pm 2.54	4.96 \pm 2.72	3.135	
Sex distribution					
Male No (%)	39(86.7)	36(80)	24(80)	$\chi^2=0.316$	0.85
Female No (%)	6(13.33)	9(20)	6(20)		
Weight in kg					
Range	43464	13.5-60	43432	T=turkeys test T1=0.008*	
Mean \pm SD	19.57 \pm 5.79	28,77 \pm 11.27	18.03 \pm 5.35	T2=0.858 T3=0.002* F=8.016	0.001*
Urinary volume/24 hr collected urine (ml)					
Range	200 -1280	200-1200	623-1710	7.69	0.001*
Mean \pm SD	670.1 \pm 382.8	653.7 \pm 316.2	1091 \pm 335.9		
Blood urea(mg%)					
Range	13 - 103	31747	18 - 32	2.724	0.77
Mean \pm SD	34.9 \pm 22.9	36.5 \pm 20.8	22.5 \pm 5.31		
Serum creatinine(mg%)					
Range	0.4-1	0.3-0.8	0.3-0.7		
(Mean \pm SD)	0.58 \pm 0.17	0.47 \pm 0.14	0.49 \pm 0.11	2.83	0.07
PRISM score					
Range	43122	43155	43178	2.7	0.25
(Mean \pm SD)	9.5 \pm 1.79	9 \pm 1.27	9 \pm 1.35		
Length of PICU stay					
(Mean \pm SD)	13 \pm 8	18 \pm 10	8 \pm 5	7.69	0.001*
Mortality: No (%)	16 (35.6)	20 (44.4)	4 (13.3)	2.724	0.022
* Significant difference. ** highly Significant difference. T1=Group 1 versus Group 2					

and 58.3±14.3, respectively; $P < 0.001$) (Table 2). The ROC curve analysis of urine NGAL values in samples collected 1 day before and on the day of AKI onset showed that urine NGAL at its cutoff level of 33.1 ng/ml could efficiently predict the development of AKI in patients complaining of sepsis, with sensitivity of 99%, specificity of 85%, positive predictive value of 99%, and negative predictive value of 90% (Table 3), (Figure 1). Table 4 summarized correlation between Neutrophil gelatinase-associated lipocalin and serum creatinine in the studied groups, Urine NGAL was not correlated with serum creatinine on the day of admission in sepsis patients (in both who developed or did not develop AKI), nor with serum creatinine on follow-up samples, after 5 days in non-AKI patients, or on AKI onset in the AKI group (Table 3). As regard

prognostic value of uNGAL (need for renal replacement therapy). The peak urine NGAL was significantly higher in patients who needed hemodialysis compared with that in those not receiving hemodialysis (53.6 vs. 46.1 ng/ml, respectively; $P < 0.001$). The AUC of the peak urine NGAL for prediction of hemodialysis was 0.81 [95% confidence interval (CI): 0.62–0.82] with a cutoff level of 48.7 ng/ml and a sensitivity and specificity of 0.84 and 0.73, respectively (Table 3).

As regard mortality predictive value of uNGAL The multivariate logistic regression analysis of the overall mortality showed that the development of septic shock [51 (35.7%) patients] [$P = 0.01$, odds ratio (OR): 11, 95% CI: 2.1–91.5] and serum creatinine ($P = 0.005$, OR: 9, 95% CI: 2.7–101) were the

Table 2: Urinary NGAL levels in patients and controls.

Urinary NGAL (Mean± SD in ng/ml)	Group 1 Sepsis, no AKI (No = 45)	Group 2 Septic AKI (No = 45)	Groups 1+2 Septic groups (No = 90)I	Control III (No=30) non septic, non AKI	P value
One day before onset of AKI	-	40.1 ± 11.7	-	-	
On the day of admission	13.5 ± 4.6	16.8± 4.3	14.8±4.2.	5.5 ± 2.6	P2=0.32 P3<0.001
On the day of sepsis	-	58.3±14.3	-	-	-
5 days after admission	15.3 ± 3.3	-	-	-	
P value	P1=0.08	P4<0.001	-	-	-

AKI= acute kidney injury;

Urinary NGAL = Neutrophil Gelatinase-Associated Lipocalin

P1= comparison between NGAL in Group 1 on the day and 5 days after admission

P 2= comparison between NGAL in Groups 1 & 2 on the day of admission

P 3= comparison between NGAL in Group 1 & 2 collectively and control group on day of admission

P4=comparison between NGAL in Group 2, one day before, on and 5 days after admission.

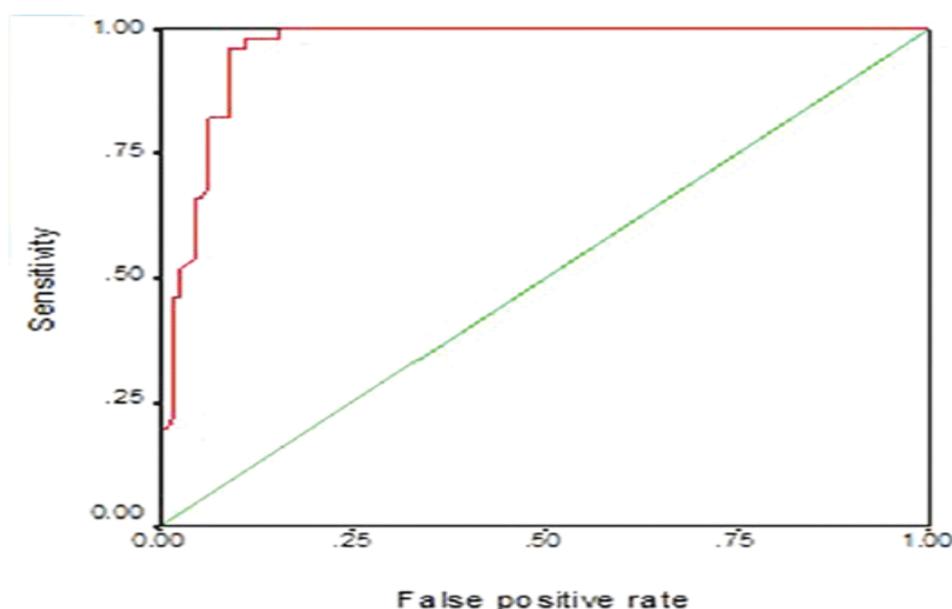


Figure 1: ROC curve for u NGAL as early diagnostic marker for AKI in septic pediatric patients.

Table 3: Validity of urine neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury

	Sensitivity	Specificity	PPV	NPV	AUC	Cut off value (ng/mL)
As diagnostic	99	85	99	90	0.96	33.1
As prognostic (dialysis indication)	84	73	99	90	0.81	48.7

ROC= Receiver Operating Characteristic Curve Analysis
 PPV= Positive Predictive Value
 NPV= Negative Predictive Value

main independent predictors of mortality. However, the peak urine NGAL or its admission values could not predict mortality (P = 0.31, OR: 6, 95% CI: 3.1–88.2) (P = 0.17, OR: 3, 95% CI: 2.9–79.9).

Table 4: Correlations between NGAL and serum creatinine

	r	P value
Sepsis, no AKI: On admission	0.35	0.026*
Sepsis, no AKI: 5 days after admission	0.2	0.19
Septic AKI: On admission	0.4	0.47
Septic AKI: At onset of AKI	0.56	0.06*

r = correlation coefficient

Discussion

Sepsis and septic shock are the biggest causes of mortality in critically ill patients [25,26,27]. The overall incidence of AKI in ICU patients ranges from 20 to 50%, with a higher incidence in sepsis patients [28]. Sepsis and septic shock both alone account for 50% or more of AKI in ICUs, and are associated with a very high mortality [29]. Like previous reported results [30] our septic patients who developed AKI were found to stay longer in the PICU compared with septic patients without AKI. Furthermore, and as found in several studies [31,32,33,34]. The development of AKI in our sepsis patients has significantly worsened the outcome compared with sepsis alone. These important findings confirm the gravity of sepsis-associated AKI, and highlight the importance of early prediction of AKI in these high-risk patients, aiming for early initiation of supportive therapy to limit the extent of renal injury and to control it by fluid resuscitation, early antibiotic initiation, and restriction of intravenous contrast dye and nephrotoxic antibiotic use. For detecting AKI, the current clinical definitions still depend on acute and relative rise in serum creatinine levels in RIFLE and Acute Kidney Injury Network criteria [20,35]. Unfortunately, creatinine elevation, the current gold standard for the diagnosis of AKI, has some limitations. Not only being delayed, but also serum creatinine is influenced by tubular creatinine secretion and by nonrenal factors such as muscle mass and liver function [36]. Furthermore, serum creatinine does not accurately reflect the glomerular filtration rate in AKI because the patient is not in steady state [37]. Additionally, reduced production of creatinine in sepsis limits its use as a marker of AKI in septic patients [38]. These limitations of serum creatinine may delay

the early diagnosis of AKI in septic patients and impede early initiation of management. To overcome this, novel biomarkers are progressively examined for the early prediction of sepsis-associated AKI. Because several studies reported that AKI occurs early in the course of sepsis, we monitored our sepsis patients since their PICU admission and during their first 5 days of ICU stay [39,40]. In our work, urine NGAL was markedly higher in sepsis patients than in controls since their PICU admission (14.8 ± 4.2 and 5.5 ± 2.6 , respectively; $P < 0.001$). In contrast, urine NGAL on admission did not differ significantly between those who developed AKI and others who did not (13.5 ± 4.6 and 16.8 ± 4.3 , respectively; $P = 0.32$). Daily follow-up of urine NGAL declared no significant change in its value in patients with sepsis who did not develop AKI, whereas in septic patients who developed AKI serum creatinine was associated and more importantly preceded by a significant jump in urine NGAL levels than on admission (on admission 16.8 ± 4.3 , 1 day before AKI 40.1 ± 11.7 , on AKI onset 58.3 ± 14.3 , $P < 0.001$). That means that AKI insult was associated and even preceded by clear earlier rise in urine NGAL than a defective delayed change in serum creatinine. More precisely, urine NGAL in our work and at its cutoff level of 33.1 ng/ml could efficiently predict AKI development at least 1 day before its onset with sensitivity of 99%, specificity of 85%, and AUC of 0.96. Explanation for this rise in urine NGAL may be due to increased renal synthesis of NGAL evidenced by upregulation of its genes early in AKI or due to the impaired reabsorption of NGAL in the proximal tubules because of tubular damage induced by sepsis [41,42,43]. An additional benefit for urine NGAL was the prediction of the need for renal replacement therapy. Urine NGAL at cutoff level of 48.7 ng/ml predicted the hemodialysis need with a sensitivity of 84% and specificity of 73% and AUC of 0.77. Unfortunately, urine NGAL could not predict intrahospital mortality. In our examined sepsis patients, urine NGAL did not correlate with serum creatinine on admission or on development of AKI. We did not include the AKI–nonsepsis group of patients in our study to report this relation in the absence of sepsis; however, it was reported before that any correlation of NGAL with serum creatinine in patients without sepsis is lost with onset of sepsis because of increased NGAL synthesis by inflammatory cells [44].

Conclusions

urinary NGAL predicted AKI well in our critically ill septic pediatric patients and also predicted their need for dialysis. This diagnostic value can be added to previous similar reports in adults and encourage its widespread use in clinical practice by promoting the daily measurement of urine NGAL at the bedside in sepsis patients with an assay kit without causing anemia as no blood is drawn daily

Recommendations

It was recommended to evaluate urinary NGAL levels as it has early diagnostic and prognostic values of AKI in septic children.

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